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REVIEW ARTICLE

Effects of Adverse Early-Life Events on Aggression and Anti-Social Behaviours in Animals and Humans

J. Haller*, G. Harold†, C. Sandi‡ and I. D. Neumann§

**Institute of Experimental Medicine, Budapest, Hungary.*

†*School of Psychology, University of Sussex, Falmer, Sussex, UK.*

‡*Brain Mind Institute, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland.*

§*Department of Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Germany.*

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We review the impact of early adversities on the development of violence and antisocial behaviour in humans, and present three aetiological animal models of escalated rodent aggression, each disentangling the consequences of one particular adverse early-life factor. A review of the human data, as well as those obtained with the animal models of repeated maternal separation, post-weaning social isolation and peripubertal stress, clearly shows that adverse developmental conditions strongly affect aggressive behaviour displayed in adulthood, the emotional responses to social challenges and the neuronal mechanisms activated by conflict. Although similarities between models are evident, important differences were also noted, demonstrating that the behavioural, emotional and neuronal consequences of early adversities are to a large extent dependent on aetiological factors. These findings support recent theories on human aggression, which suggest that particular developmental trajectories lead to specific forms of aggressive behaviour and brain dysfunctions. However, dissecting the roles of particular aetiological factors in humans is difficult because these occur in various combinations; in addition, the neuroscientific tools employed in humans still lack the depth of analysis of those used in animal research. We suggest that the analytical approach of the rodent models presented here may be successfully used to complement human findings and to develop integrative models of the complex relationship between early adversity, brain development and aggressive behaviour.

Key words: maternal separation, peripuberty, social isolation, emotionality, HPA axis, oxytocin, vasopressin, serotonin

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Correspondence to:
I. D. Neumann, Department of Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Universitätstrasse 30, 93953, Germany (e-mail: inga.neumann@biologie.uni-regensburg.de).

Introduction

Current explanations for the development of violence and antisocial behaviour emphasise the importance of early factors, which, in conjunction with genetic predispositions, have a large role in shaping behaviours displayed in adulthood (1–3). Although neuroscientific evidence clearly shows that early-life events have a strong impact on brain development, eventually modifying the subsequent behavioural phenotype (4–7), the interaction between early adversities, brain development and behaviour are still poorly understood. Although recent advances in brain imaging techniques opened an important new window for understanding the neural underpinnings of aggressive behaviour (8), animal models remain valuable tools for disentangling and dissecting the contribution of particular neurobiological factors because they are devoid of the human cultural influences.

Several animal models have been developed to capture cardinal features of early adversity-induced aggression in humans and to study the underlying endocrine, neuronal, genetic and epigenetic mechanisms. These models are centred on stressors delivered during critical periods of early life (e.g. the period of maternal care, weaning and puberty). The relevance of these models for aggression research was greatly enhanced by the recent introduction of new behavioural techniques, which detached from the classical approach of studying natural aggressiveness by mimicking aetiological factors of aggression-related psychopathologies and by identifying deviant

Table 1. A Summary of Behavioural and Emotional Features of Rodents Submitted to Three Models of Early-Life Stress: Repeated Maternal Separation, Post-weaning Social Isolation and Peripubertal Stress.

			RMS		PwSI		ppS	
Behavioural and emotional features			Juven	Adult	Juven	Adult	Juven	Adult
Aggression	Intensity		↑	↑	↑	↑		↑
	(Abnormal) attacks on:	Inoffensive opponents						↑
		Females						↑
		Vulnerable targets				↑		↑
	Relational abnormalities	Deficient signalling				↑		
		Offensive ambiguity	↓	↓		↑		↔
Emotional behaviours	Anxiety			↑		↔	↓	↑
	Depression			↑		↔	↓	↑
	Sociability		↓			↓		↓
Stress responses	Glucocorticoid		↑	↑		↑		↘
	Autonomic					↑		

↑, increase; ↓, decrease; ↘, signs of decrease; ↔, no change; juven, adult, features shown in juveniles or in adulthood; deficient social signalling, attack not preceded by threats (sudden attacks while the attacker explores the environment, sniffs at opponent, shows self-grooming or submissive posture); inoffensive opponents, or narcotised/submissive adults; offensive ambiguity, offence and defence intermingled while dominance is reduced or attacks increased against smaller intruders but decreased against larger intruders; RMS, repeated maternal separation; pwSI, post-weaning social isolation; ppS, peripubertal stress, vulnerable targets: head, throat, belly, paws, testicles. Empty cells: not investigated so far.

forms of aggression that arise as a consequence of these treatments. Deviant features include mismatches between provocation and response (aggression exceeds species-typical levels), disregard of species-specific rules (attacks on inoffensive opponents and females or aiming attacks towards vulnerable body parts) and abnormal relations between the contestants (deficits in social signalling and offensive ambiguity) (Table 1) (9,10). Behaviours fulfilling these criteria are perceived as deviations from the 'natural rules' that govern aggression in animals, and resemble important aspects of aggression-related psychopathologies.

We strongly consider that the control of aggression cannot be understood without integrating animal findings of translational value and human findings. Close interactions between the two sides offers human research the chance to take advantage of the depth of analysis allowed by the advanced neuroanatomical and neurofunctional methodologies currently used in animal research, whereas research on animal aggression will greatly benefit from incorporating information on the phenomenon it models. Therefore, we here review early developmental factors that engender violent and aggressive behaviour in humans and present three selected developmental models of rodent abnormal aggression that mimic specific early aetiological factors of aggression: repeated maternal separation (RMS), post-weaning social isolation and peripubertal stressors. The presentation of models follows the same structure to ease their comparison.

Early-life factors contributing to antisocial behaviour in humans

Although the prevalence rates of antisocial behaviour, conduct problems and general aggression in human populations are well documented (11,12), understanding of the mechanisms that underlie individual differences in adolescent and early adult antisocial behaviour remains relatively rudimentary. Theoretical explanations offered to account for the transmission of these influences and associated interactive processes fall into two primary domains: (i) intergenerational transmission hypotheses and (ii) family socialisation hypotheses. Advocates of an intergenerational transmission perspective emphasise the importance of early susceptibility factors (genetic predisposition, prenatal and early postnatal environmental influences and their epigenetic manifestation) as a point of origin in understanding the expression and development of psychopathology in children, adolescents and adults (13). Advocates of a family socialisation perspective emphasise the importance of contextual influences, such as harsh parenting practices, as antecedents of later antisocial behaviour (14,15). Common to both intergenerational transmission and family socialisation perspectives is the increasing application of a process-oriented perspective, such that emphasis is placed on the identification of mediating and moderating processes underlying specific early risks and the onset and development of later antisocial behaviour problems.

Early manifestations of antisocial behaviour in humans

There is now substantial evidence that precursors to psychiatric problems such as conduct disorder, oppositional defiant behaviour/disorder and attention deficit hyperactivity disorder are evident in children as young as 2 or 3 years of age (16,17). To understand the development of psychiatric symptoms in adolescence and early adulthood, it is necessary to identify the temperamental characteristics in children that are associated with later behaviour problems or psychiatric disorder. In general, specific early child temperamental characteristics can indicate an elevated risk for the development of later disruptive behaviour problems. This is most evident for children aged 3 years old and older, although some studies have found effects for children as young as 2 years. The temperamental

precursors to externalising disorders include an inability to inhibit behavioural responses to stimuli (behavioural disinhibition), fearlessness and high negative reactivity or emotionality (18,19). A handful of studies have followed children from early childhood in an effort to characterise trajectories of behaviour problems. These studies have found evidence for consistency in disruptive behaviour problems from early to middle childhood and adolescence, with increased predictive ability when the earliest ages of assessment are aged 3 years rather than 2 years (17,20). Detailed reviews of the literature on early prediction of later disruptive behaviour have reported that, to date, there are only modest links between infancy and adolescent behaviours (21). One difficulty in identifying children early for disruptive behaviours is that behaviours such as aggression and other disruptive behaviours are common during early childhood, thus increasing the likelihood that children could be identified at-risk but subsequently do not develop elevated symptoms. Despite these concerns, children who develop psychiatric symptoms within the externalising spectrum (aggressive behaviours through to antisocial behaviour disorder) appear to have identifiably different temperamental traits than children who do not develop such disorders and from children who develop psychiatric symptoms along the internalising spectrum (anxiety, depression, etc.).

Neuroendocrine processes underlying antisocial behaviour in humans

There are clear indications that a fundamental feature of the early brain in response to chronic and severe stress exposure is dysregulated neurobiological functioning (22). In human studies, cortisol secretion is typically studied in relation to hypothalamic-pituitary-adrenal (HPA) axis activation, and heart rate and skin conductance responses are used as markers of autonomic activity. The HPA axis is a stress mobilisation system that varies in tonic activation over the course of the day (i.e. peak in the morning followed by decline) and plays a key role in mounting a response to physical and psychological stressors (23). Typically measured through circulating cortisol levels, basal HPA activity that is either too high or too low may signal problems. As described by the adaptive calibration model of stress system development, HPA activation may adapt upward or downward to manage sustained adversity, each of which comes with costs to physical and psychosocial functioning (24,25). Studies of antisocial adults have observed a negative relationship between cortisol levels and behavioural dysregulation (26). Hypotheses proposed for this inverse association suggest that such individuals may be physiologically under-aroused, that the negative-feedback mechanisms acting on the HPA axis are hypersensitive, or that they have an increased threshold for stress (27). Few studies have been conducted on cortisol levels or the cortisol response to stress in aggressive children, and there have been equivocal findings across studies. Some studies have found associations between reduced basal cortisol concentrations and aggressive behaviour (28), other studies found no such relationship (29), with others noting a positive relationship (30). An important caveat to these studies comprises differences in the measurement of cortisol activation that may underlie differences in the pattern of association with the antisocial behaviours reported.

A core limitation of past research examining neurobiological processes underlying the development of antisocial behaviour in humans is that the vast majority of findings derived from human studies have been generated from correlational research designs, thereby precluding causal inferences relating to the role of cortisol activation underlying human aggression. There have been very few studies with a design that is capable of showing that low cortisol levels indeed precede the onset of antisocial or aggressive behaviour throughout adolescence and into young adulthood. An exception to this dearth of evidence, and which highlights a longitudinal (albeit noncausal) link between low cortisol levels and aggressive behaviour, is the finding that low cortisol was moderately predictive of aggressive behaviour 5 years later and, furthermore, that this relationship appeared to be mediated by the effects of cortisol on personality attributes marked by self-control deficiencies (31). Another longitudinal study (32) showed that clinic-referred boys with consistently low cortisol levels in samples obtained 2 years apart demonstrated the highest levels of aggression and conduct disorder symptoms over time. Studies focusing on parents and children suggest a degree of heritability in cortisol levels. For example, parent antisocial personality symptom counts have been shown to be inversely related to cortisol concentrations and positively with conduct problems in children (33). This suggests that cortisol may be involved in the intergenerational transmission of antisocial behaviour and provides further indirect evidence that this steroid plays a role in antisocial behaviour (22,34).

Taken together, these findings suggest that emotional features reflected by autonomic and glucocorticoid stress responses are important contributors of aggression-related psychopathologies.

The influence of adverse early-life events on aggression and antisocial behaviour in humans

Two primary domains of the postnatal rearing environment have been shown to influence antisocial behaviour problems: parenting and inter-parental conflict, with negative extremes in each domain representing child maltreatment. Parental lack of sensitivity (35,36), rejecting parenting (17), maternal hostility (37,38) and maternal control (38) have each been associated with disruptive behaviours in early childhood, a known precursor to antisocial behaviour. Exposure to frequent, intense and poorly resolved inter-parental conflict makes unique contributions to later behaviour problems in children both directly and in interaction with children's emotional reactivity (39). Maltreatment has been associated with long-term changes in the neuroendocrine stress systems, specifically HPA axis dysregulation (40). Longitudinal evidence suggests that adults who were maltreated as children show basal cortisol and HPA axis dysregulation compared to non-maltreated controls (40,41). Inter-parental conflict also predicts children's conduct problems, with associations as a result of genetic and nonshared environmental influences (42). Evidence also suggests that genetically-influenced aversive temperamental characteristics in childhood may also play a role in exacerbating the effects on the postnatal environment. For example, such behaviour might tax parents' patience and regulated attention. Aversive parental responses might, in turn, serve as antecedents of later externalising problems, particularly when contextual supports

are also lacking (14,43). Continuity in these reciprocal pathways to externalising behaviour is moderate to strong, beginning at age 2–3 years, extending through school age (17,18) and early adulthood (16,44). For example, by age 3 years, children rated as high in irritability, fearlessness and emotional labiality have been found to be three times more likely to meet criteria for DSM-IIIR antisocial personality disorders at 18 and 21 years than 3-year-old children with normative scores on these dimensions (44). However, there is clear evidence that psychosocial interventions that target parenting practices can reduce the risk for antisocial behaviour problems, even among highly delinquent populations (45).

From the point of view of the models presented below, three types of adverse early-life events appear to be especially important. A lack of tight bonds with parents or care takers (early emotional neglect), social exclusion and loneliness (early social neglect), and exposure to stress during childhood and puberty are all associated with an increased risk of developing a broad number of psychiatric disorders (41,46). All three also emerged as predictors and worsening factors of externalising problems and are considered to significantly contribute to the expression of violence and antisocial behaviour from childhood into adulthood (47–52).

Neuronal background

Numerous neuronal explanatory models of human abnormal aggression were developed over the last decades. Despite the large number of such attempts, no consensus was reached regarding the neuronal underpinnings of aggression-related psychopathologies. One group of models emphasises the role of cognitive and emotional processes and identifies disrupted prefrontal and amygdala functioning as the neuronal substrates of this type of malfunctioning (53–55). Other models can be perceived as attempts to integrate higher-order neural/psychological functions and lower-order executive mechanisms (e.g. those residing in the hypothalamus and central gray) (56,57). Recently, an almost 'purely' neural theory of human aggression was also developed (58). The circuitries hypothesised to underlie abnormal forms of aggression are overall similar, although the models are discrepant regarding both the brain areas included in the circuitries and their particular roles. A subgroup of these theories suggests that the two major types of human aggression, namely reactive and instrumental aggression, result from different neuronal malfunctions, which derive from specific developmental trajectories (56,57,59).

Importantly for the present review, the animal models presented below may successfully be used to reveal the interactions between developmental (i.e. genetic and environmental) factors, the types of aggression resulting from these and the particularities of underlying neuronal mechanisms.

Caveats in the study of human aggression and antisocial behaviour

A significant limitation of past research in the study of the family-based origins of aggression and antisocial behaviour is a predominant reliance on biologically related parents and offspring. In biological families, associations between parent and child characteristics may result from an underlying shared genetic characteristic that simultaneously influences both the trait in the parent and the trait in the child. Precisely because these shared genes influence the behaviours of both parent and child, it is not possible to unambiguously disentangle whether parent-to-child influences are a result of shared genetic effects, family environmental influences, or both. Although the interplay between genetic and environmental factors has been examined historically using twin-based research designs, twin studies assume that monozygotic (from the same fertilised ovum) and dizygotic (from two separately fertilised ova) twin pairs share environment to the same extent, and so a greater degree of concordance in monozygotic pairs is attributed to genetic factors. However, it has been shown that the environments children experience may vary distinctly even when children are genetically identical. Recent studies using adoption-based research designs have advanced insights in this area of study and are showing specificity of parent and family level influences on children's antisocial behaviour problems (60,61). Understanding the interplay between genetic, prenatal, neurobiological and postnatal factors on the aetiology of antisocial behaviour remains an area of continued scientific, practice and policy relevance. In a case study of conduct disorders in the UK, it was estimated that preventing conduct disorders in the most disturbed children would save around £150 000 of life time costs per case (£5.25 billion). An extension of this figure to international impact rates makes a substantial case for continued investment in the promotion of understanding relating to the causes, mechanisms and potential intervention sites aimed at remediating human antisocial behaviour.

One possible way of filling up caveats in the study of human aggression is the use of animal models. Below, we provide an overview of the findings obtained with three such models, each mimicking one particular aetiological factor that was shown to play a role in the development of human violence and antisocial behaviour (i.e. RMS, post-weaning social isolation and peripubertal stress). With each model, several questions are addressed. Does the aetiological factor alter aggressive behaviour? Are abnormal features detectable? Is the model associated with changes in emotionality? And, finally, how are aggression-related brain functions altered by exposure to early adversity? The common characteristic of the models presented below is the relative uniformity of consequences within groups of subjects submitted to the very same model. This contrasts to the large individual variability seen in humans, which is a result of the high complexity of interacting biological and environmental factors shaping the individual behavioural development, including genetic and epigenetic processes; prenatal neuroendocrine factors; maternal and paternal behavioural contributions; and, specifically, postnatal stress experiences (7,62).

Although we are well aware that the focus on the three rodent models has limitations (i.e. early-life events are more complex in nature), this particularity, which is likely explained by homogenous genetic backgrounds and standardised maintenance conditions, may be considered as an asset in that it permits an analytical approach (i.e. the dissection of the role of particular aetiological factors).

The animal model of maternal separation

One of the best characterised rodent models of adverse early-life experiences, mirroring adverse human childhood experiences such as emotional neglect and social deprivation, is the separation of pups from their mother. There exist various paradigms of maternal separation for rats and mice, including (i) a single separation of the litter from the dam for 24 h within the first week of life (63–65); (ii) early social deprivation of the pups by separating them from both the dam and the littermates for several hours per day (66,67); and (iii) repeated maternal separation (RMS) by daily separation of the whole litter from the dam for up to 3 h during the first 2 weeks of life (68–70). Numerous maternal separation effects were described not only on juvenile or adult social behaviours, but also on emotionality, cognitive functions, physiological and behavioural stress coping, ethanol preference, and associated neuroendocrine and neuronal adaptations, as outlined in more detail below (71,72). In general, the effects were revealed to strongly depend on the particular paradigm employed, species, strain and gender (69,73–75). Therefore, it is not surprising that there are also varying and partly controversial reports on long-term and epigenetically driven consequences of maternal separation (76,77). Here, we focus on RMS as an established and extensively used rodent model for early social life stress, which has been shown to fulfil the criteria of face, construct and predictive validity.

Impact of RMS on aggressiveness

RMS has been used to investigate early-life stress-induced alterations in various social behaviours, including play-fight behaviour (social play) and intermale aggression in juvenile, adolescent and adult male rats or mice. Social play is seen in most species and a prerequisite for the development of adequate adult social behaviours (78–80). The behavioural patterns displayed by rat juveniles, such as nape attacks, pinning and supine postures, are related to adult social, aggressive and sexual behaviour, although they differ substantially from adult behaviours with respect to intensity, quality and contextual settings (81). As expected, juvenile rats show the highest level of social play, whereas we found a sharp decline in the duration and frequency of play-fight behaviour at adolescence, which was almost invisible in adult male rats (82). Exposure of rat pups to RMS significantly affected the development of social play compared to nonseparated controls. Specifically, male juvenile and adolescent RMS offspring spent less time with playful social interactions but showed a higher frequency of nape contacts towards the unknown age-matched play partner at age of 5 weeks. Moreover, juvenile RMS rats showed more vigorous fur pulling and less supine postures towards the play partner. Because the total duration of play-fight did not differ between RMS and control rats during the 10-min test session, RMS may not affect spontaneous social play motivation but, rather, shifted the specific elements of social play into a more dominant, rougher and more aggressive direction. The lower number of supine postures in juvenile RMS rats further suggests that RMS rats avoid submissive postures. Taken together, the behavioural patterns seen in juvenile offspring exposed to early-life stress by RMS can be interpreted as inappropriate social play behaviour including rather aggressive elements.

The effects of RMS experience on social behaviour continue into adulthood, because RMS rats generally displayed a higher level of aggressive behaviour, when confronted with a male intruder in their home cage during a 10-min resident–intruder (RI) test (83). The excessive aggression of RMS rats was specifically reflected by the display of lateral threat, offensive upright and keep down. However, it is not yet clear whether adult RMS rats also display more abnormal aggressive behaviour, which remains to be investigated. Also, species-specific consequences of RMS on adult aggression appear to exist. Despite the similar RMS-induced increase in anxiety- (plus-maze) and/or depression- (forced swim test) related behaviours in both Wistar rats and C57BL/6 mice, RMS induced a decrease in adult intermale aggression in mice reflected by longer attack latencies (84). In support, RMS exposure was recently shown to suppress male aggression in peripubertal C57BL/6J mice, and this was accompanied by reduced plasma testosterone, reduced arginine vasopressin (AVP) and increased oxytocin (OXT) hypothalamic immunoreactivity (85).

Impact of RMS on emotionality

RMS is an established rodent model for anxiety- and depression-related diseases. It consistently results in increased anxiety levels, and behavioural dispair or depression-related behaviour in the forced swim test reflected by passive stress coping, decreased exploration of a novel environment and increased acoustic startle responses (69,70,83,86–90). Antidepressant treatment was shown to partly reverse these behavioural consequences (87,91). Also, RMS-exposed mice show a higher vulnerability to chronic psychosocial stress in adulthood with respect to emotional, physiological and immunological stress parameters (92). Thus, in a chronic psychosocial stress model of chronic subordinate colony housing, the most severe chronic stress-effects were seen in those adult mice that had been exposed to RMS. Because we found a lower level of aggression associated with a more passive stress-coping style in adult RMS mice, it is most likely that adult RMS mice of that study tended to be more submissive as a result of exposure to the dominant male mouse during the chronic psychosocial stress exposure with the consequence of more severe stress effects.

Neuronal background

The above mentioned behavioural alterations induced by RMS are accompanied by long-lasting and epigenetically driven alterations in various neurotransmitter, neuropeptide and hormonal systems (71,72,93–95). For example, an increased (re)activity of the HPA axis reflected by elevated mRNA expression of corticotrophin-releasing hormone (CRH) in the hypothalamic paraventricular nucleus (PVN) and increased plasma adrenocorticotrophin (ACTH) and corticosterone concentrations in response to an acute stressor (68,69,82,83,87,96) were found in adult RMS rats. Also, after postnatal stress, juvenile rats have elevated (i.e. adult-like) levels of

basal plasma corticosterone compared to juvenile control rats. Thus, the increase in plasma corticosterone observed during a single separation period (65,97) appears to be extended throughout the juvenile period and is likely to impact on brain development, including the maturation of social and emotional behaviours. Accordingly, the elevated corticosterone levels might be causally related to the increase in offensive social play observed in male juveniles exposed to RMS, similar to the observation that circulating corticosterone determines adult intermale aggression, as shown in experiments involving the acute blockade and replacement of corticosterone, as well as with glucocorticoid receptor blockers (83,98–102). For example, an acute rise in plasma corticosterone promotes aggression via fast and thus nongenomic effects (102) and may contribute to the escalation of violent behaviour under stressful conditions (101). However, monitoring of ACTH and corticosterone responses to an aggressive encounter or a nonsocial stimulus is still needed in RMS juveniles; although the elevated ACTH response to forced swimming in adult RMS rats indicates changes in the HPA axis regulation as a result of RMS.

In addition to HPA axis alterations, RMS-induced changes were also described for neuropeptidergic systems such as the AVP and OXT systems. Both AVP and OXT are key players in the regulation of a wide variety of social behaviours, including intermale and maternal aggression, affiliation, sexual behaviours and social cognition (103–107). The expression of their receptors (i.e. the V_{1A}-R and OXT-R) develops in a brain region-specific manner from the juvenile period to adolescence into adulthood (108,109), suggesting their particular role in the maturation of social behaviours. Exposure to RMS severely interfered with these developmental adaptations, which is likely to underlie the alterations in aggressive behaviours after RMS exposure. For example, exposure to RMS increased V_{1A}-R binding in the piriform cortex in adolescent and adult rats and in the lateral septum in juveniles, and decreased OXT-R binding in the agranular cortex (juveniles and adolescents), the lateral septum (adults) and the ventromedial hypothalamus (adults) (108).

In addition to AVP and OXT receptors, differences in local gene expression, immunoreactivity and release patterns of AVP and OXT have also been associated with differences in adult aggression (110–116). With respect to early-life stress, the increase in aggressive play-fight behaviour and in adult aggressive behaviour in RMS rats was accompanied by a significant higher AVP mRNA expression and AVP immunoreactivity in hypothalamic areas such as the PVN, supraoptic nucleus and lateral hypothalamus. In adult rats, this increase was not seen under basal conditions, although a more pronounced rise in hypothalamic AVP expression was found in RMS rats in response to exposure to the RI test compared to nonseparated control rats (82,83). Unexpectedly, a similar increase in AVP mRNA expression in the PVN was also found in adult male RMS mice despite the fact that they showed less aggression (114). This indictates the possibility of the primary effects of RMS on anxiety, which may in turn modulate aggression in a species-specific manner (115). The long-lasting rise in basal AVP expression found in adult RMS rats was found to be a result of epigenetic modulation of the AVP gene (93).

In extension of its many pro-social effects, OXT has recently been described to exert anti-aggressive effects in male (107) and female (116) rats. Also, the OXT system is sensitive to adverse early-life experiences as described above. However, whether the RMS-induced increase in intermale aggression is indeed accompanied by alterations in brain OXT neurotransmission including changes in local OXT-R binding needs to be demonstrated. The human findings of a negative correlation between basal plasma or CSF OXT levels and aggression and childhood traumatisation (41) further suggest a dysregulation in the OXT system caused by early-life stress.

The serotonin (5-HT) system also significantly contributes to the regulation of aggressive behaviours and is sensitive to early-life stress (117,118). In this context, an interaction effect between childhood environment and the 5-HT transporter genotype on violent behaviour was found (119,120). In agreement with the general view that 5-HT exerts an inhibitory control over impulsive aggression (121–124), we found a reduced 5-HT immunoreactivity in the anterior hypothalamus in RMS-treated rats, suggesting a decrease in local 5-HT release associated with increased aggression (83). Furthermore, a negative correlation was revealed between 5-HT immunoreactive staining (e.g. in the anterior hypothalamus) and the duration of lateral threat in RMS rats (83). Thus, because a balanced activity of the 5-HT system within the anterior hypothalamus appears to be critical for the development of appropriate aggressive behaviour, RMS-induced alterations in the activity of the 5-HT system are likely to contribute to the elevated levels of intermale aggression seen after exposure to RMS.

Conclusions

The rodent model of RMS has been proven to be a suitable paradigm to reveal the effects of early-life neglect on juvenile and adult intermale aggression and the underlying neurobiological mechanisms. Exposure to RMS resulted in more aggressive play-fight behaviour in juvenile and increased intermale aggression in adult rats and was shown to be accompanied by alterations in the AVP and 5-HT systems. Whether RMS also induces alterations in the quality of aggression and a shift towards abnormal aggression needs to be shown. Also, provided that a suitable behavioural test for female (non-maternal) aggression is employed, such as the female intruder test (116), the RMS paradigm appears to be suitable for studying sex-specific differences in RMS-induced alterations in juvenile or adult aggression.

The animal model of post-weaning social isolation

Scientific interest in early social relationships was prompted by the seminal studies of Harlow (1965) (116a) who showed that the social isolation of monkeys in early life 'obliterates the animals socially' and results in a sequence of symptoms that resemble those seen in children who experience poor parenting, social exclusion and loneliness. In rats, post-weaning social isolation models early social neglect by eliminating social contacts with peers from weaning into early adulthood. Rodents submitted to this paradigm show

strong signs of social incompetence as adults (diminished ability to integrate in groups) (125) and display quantitative and qualitative changes in aggressive behaviour that are in many respects similar to those induced by early social neglect in children (126,127). Taken together, these considerations demonstrate the construct validity of the model.

Impact of post-weaning social isolation on aggressiveness

Effects on aggression were best described in male rats reared in isolation after weaning [postnatal day (PND) 21 to PND 80]. When faced with opponents in their home cage, such rats show enhanced levels of aggression as demonstrated by an increased number of bites delivered to opponents (127). This feature may not be considered abnormal *per se* because differences from controls are not particularly dramatic (128). In addition to quantitative changes, however, a series of qualitative behavioural changes also develop. Rats reared in isolation preferentially target their bites onto vulnerable body parts of opponents (head, throat and belly). Unusual attack targeting is associated with marked deficits in attack signalling by offensive threats. Moreover, the two features appear correlated: the more bites that are delivered to vulnerable targets, the less likely are these preceded by social signals (127). Thus, post-weaning social isolation leads to the emergence of dangerous forms of attack, which are poorly predictable for opponents because of deficient social signalling. Abnormal attacks are associated with other features indicative of disrupted behaviour. By contrast to controls, socially isolated rats show strong signs of behavioural agitation evidenced by rapid switches from one behaviour to another; moreover, their high aggressiveness is associated with increased defensiveness, which is a prominent feature of emotionally laden aggressive behaviours deriving from early social neglect (127). Changes in aggressiveness develop rather rapidly in rats, as shown by increased play-fighting after just 4 weeks of post-weaning social isolation (i.e. around PND 50) (129).

The impact of isolation rearing on aggression was less well characterised in other species. In mice, this condition increased the duration of offensive threats (130); in another study, mice isolated from weaning attacked opponents in neutral arenas, a behaviour that was absent in controls (131). Thus, mice reared in isolation displayed aggression in a context where this behaviour is not normally expressed, which may be considered as an abnormal feature. In gerbils, post-weaning social isolation increased both offence and defence, which replicates the behavioural ambiguity (parallel increases in offence and defence) seen in rats (132). Taken together, these studies suggest that post-weaning social isolation results in abnormal forms of aggression in rats and several other rodent species.

Noteworthy, disrupted behaviour appears to be highly persistent. Exposing isolation-reared rats to three encounters over 6 days (PND 80–86) did not result in significant behavioural changes over time (133). Moreover, abnormal attack features persisted after 3 weeks of re-socialisation (social isolation: PND 21-80; aggression-testing: PND 80; re-socialisation: PND 80-101; re-testing for aggression: PND 104 (125).

Impact of post-weaning social isolation on emotionality and stress responsiveness

Basal glucocorticoid levels and heart rates were evaluated at multiple time-points after weaning in isolation-reared rats and no differences from controls were noted (130,132,133). By contrast, acute autonomic and glucocorticoid responses to aggressive encounters markedly increased (133). Because Weiss *et al.* (134) did not show comparable effects with nonsocial stressors, we recently studied rats in the open-field, elevated plus-maze, forced swimming, social interaction and RI tests (135). No consistent changes were observed regarding anxiety and depression-like behaviours. With regard to stress responses, nonsocial tests did not and social tests did increase glucocorticoid levels over those seen in controls, suggesting that rats isolated from weaning are particularly sensitive to social stressors. Similar findings were obtained in humans, where early social neglect-related HPA-axis dysfunction was most evident in social contexts (136,137).

Neuronal background

To evaluate the neural background of abnormal aggression shown by rats reared in isolation, first we investigated brain c-Fos expression profiles in rats exposed to the RI test (138). Brain areas normally involved in the control of territorial aggression (BNST, medial and lateral amygdala, and the mediobasal hypothalamus) and stress-related structures (PVN, locus coeruleus) were over-activated compared to controls. These findings are in line with theories on the neural control of human reactive aggression that is highly emotional and is considered to result from the over-activation of the amygdala and mediobasal hypothalamus (57). Interestingly, however, the prefrontal cortex, which is generally considered to limit aggressive behaviour, was also over-activated by post-weaning social isolation. This unusual finding prompted a second study that specifically focused on the prefrontal cortex. Rats reared in isolation showed reduced prefrontal volumes and reduced glia counts. Interestingly, these deficits were restricted to the right-hand side of the prefrontal cortex, similar to highly aggressive humans; moreover, the magnitude of change (10–15%) was also similar (139). Still, the prefrontal cortex was markedly over-activated by aggression in isolation-reared rats. These paradoxical findings mirror those obtained in humans submitted to simulated aggressive conflicts that resulted in reactive forms of aggression. Under such conditions, the activation of the prefrontal cortex and the level of aggressiveness showed a positive correlation (140–144). Thus, post-weaning social isolation-induced abnormal aggression is associated with chronic deficits in prefrontal functioning but enhanced acute responses to aggression in this brain area.

Conclusions

Post-weaning social isolation is followed by profoundly altered patterns of aggression, characterised by natural rule-breaking (e.g. attacks on vulnerable targets and poor social communication), offensive ambiguity (parallel increases in offence and defence) and

behavioural agitation in adulthood. Alterations in behaviour are associated with enhanced physiological responses to social stressors, deficits in prefrontal development and the over-activation of brain areas that acutely control aggressiveness. The behavioural/emotional/neuronal profile of rodents submitted to this model resembles that seen in human reactive aggression, which, most notably, often results from early social neglect. As such, the model appears to represent a useful tool for studying the developmental aspects of human reactive aggression.

The animal model of peripubertal stress

Given the profound hormonal and neurodevelopmental changes occurring around puberty, the brain is during this period highly susceptible to environmental perturbations, such as stress exposure (145,146). Early rodent studies indicated that stress exposure during puberty increases agonistic behaviours during adolescence (147,148). Elegant work in male golden hamsters has shown that exposure of social stress or social subjugation (i.e. social defeat) during puberty enhances offensive aggression and accelerates the transition from play-fighting to adult aggression (149). However, stress in these studies was induced through confrontations with other conspecific animals, therefore precluding the exclusion of social learning as a critical factor in the development of pathological aggression. Recently, a rat protocol based on exposure to fear-inducing experiences (predator odour and exposure to an elevated platform) during the peripubertal period (on scattered days during the period comprising postnatal days P28–P42), and excluding social learning factors, was shown to be a valid model for pathological aggression, including intimate partner violence, with face, construct and predictive validity (150,151). This peripubertal stress rat model of pathological aggression leads to enhanced aggression not only in males (150,151), but also in peripubertally stressed female rats (152). Below, the characterisation and implications of this model are specifically addressed.

Impact of peripubertal stress on aggressiveness

Male rats submitted to fearful experiences during peripuberty exhibit an overall pattern of pathological aggression (151–153) according to the criteria summarised in the Introduction to the present review. Specifically, (i) peripuberty stressed male rats persist in attacking opponents even when they display clear submissive positions (a behaviour not observed in controls); (ii) they target vulnerable body parts; and (iii) they attack individuals that do not pose a real threat (i.e. smaller or anaesthetised males, as well as females) (151–153). These findings fit with human studies showing that children exposed to stress show increased risk to develop subsequent aggressive behaviour (120,154). Increased aggression towards a male conspecific, as evaluated in the RI test, was also found when, instead of stress, animals were injected with a stress dose of corticosterone (5 mg/kg, daily) on the same days when animals are stressed in the peripuberty stress protocol (155). Remarkably, in addition to their more aggressive behavioural pattern at adulthood, animals treated with corticosterone at puberty already displayed increased play-fighting during adolescence, suggesting that the enduring effects observed might be the consequence of more immediate effects in social behaviours potentially affecting the neurodevelopmental trajectory of corticosterone-treated animals (155). These observations are in line with findings in the golden hamster showing that accelerated transition from play-fighting to adult aggression: (i) is accompanied by daily increases in plasma cortisol levels when induced by exposure of juvenile males to social subjugation (156) and (ii) was also induced when social stress was substituted by daily injections of glucocorticoid agonists (i.e. dexamethasone or cortisol) (149,157) that could be antagonised by co-treatment with a glucocorticoid receptor antagonist (149).

Interestingly, females are also susceptible to increased programming of aggressive behaviour by peripuberty stress (152). Peripuberty stressed females show increased aggression toward females, both during dioestrus and oestrus, as well as towards a male partner during their first encounter. These females also show increased maternal aggression against a male intruder. These findings fit with human reports showing that the probability to develop personality disorders accompanied by aggression is increased by exposure to adverse experiences during childhood not only in boys, but also in girls (158,159).

Impact of peripubertal stress on emotionality

In addition to leading to pathological aggression, exposure to peripubertal stress in rats has, as well, a profound impact in different aspects of emotionality. Intriguingly, the effects are paradoxically different when examined during late adolescence and at adulthood. At adolescence (studied during P45–P51), peripuberty stress leads to decreased anxiety-like behaviour, as evaluated in the elevated plus maze and open field, both in males and females (160), which is in contrast to the increased anxiety-like behaviour displayed by these animals at adulthood (152). In addition, during late adolescence, peripuberty stressed animals show increased risk-taking and novelty-seeking behaviours (160). However, and different from what is reported during adulthood (151), peripuberty stressed rats do not show symptoms of depressive-like behaviour (measured at the forced-swim test), nor changes in the corticosterone response to stress when evaluated at adolescence.

At adulthood, in addition to the enhanced signs of aggression, anxiety- and depression-like behaviours indicated above, peripuberty stressed male rats exhibit reduced sociability, as indicated by their reduced exploration of a juvenile conspecific in the three-chambered test (151). This pattern of behavioural changes is reminiscent of the findings reported in humans exposed to traumatic stress during equivalent developmental periods (i.e. childhood and puberty) (161). In humans, depression and enhanced aggression are frequently comorbid, particularly during adolescence and early adulthood, and both have been associated with early-life stress (162,163). Importantly, when the same stress protocol used during peripuberty is applied at adulthood, no behavioural effects (in aggression or emotionality) are observed, which strongly supports the view that peripuberty is a period of special sensitivity to the behavioural programming of aggressive and emotional behaviours by stress (151).

At the hormonal level, peripuberty stress was found to lead to a reduced corticosterone response towards the end of the stress protocol (151), an effect also observed in response to mild stress in adult animals treated with corticosterone during the peripuberty period (155). These data fit with studies in humans showing that stress exposure during peripuberty is associated with lower cortisol in adulthood (164). Blunted cortisol responses have been frequently found in post-traumatic stress disorder patients (165,166), and progressive attenuation of cortisol across age was reported in victims of childhood sexual abuse (167). Moreover, peripuberty stress in rats was also found to lead to an increased plasma testosterone/corticosterone ratio measured after the RI test (151), resembling human data in violent individuals (168).

Neuronal background

Peripuberty stress in rats leads to changes in the activity of corticolimbic circuits that can be already observed during the late adolescence period following stress exposure. More precisely, these adolescent rats show increased metabolic rates in the hippocampus, basal amygdala and cingulate cortices when exposed to fear cues (169). At adulthood, enhanced activity in the amygdala is still observed, whereas a blunted response of the medial orbitofrontal cortex is demonstrated immediately after the RI test (151). This pattern of brain activity is reminiscent of findings of amygdala hyperfunctioning and medial orbitofrontal cortex hypo-functioning in humans with impulsive aggression (170,171).

In addition, peripuberty stressed rodent males showed enhanced expression of the monoamino oxidase A (MAO_A) gene in the prefrontal cortex, whereas treatment with a MAO_A inhibitor prevented the emergence of pathological aggression (151). MAO_A gene variants have been found to increase the risk of antisocial and aggressive behaviours following childhood adversity (4,120,154). However, subsequent investigations showed that extreme levels of early-life stress can lead to increased aggression independently of MAO_A or other 5-HT-related genetic variations (notably, the 5-HT transporter) (120,154).

Strikingly, the observed changes in brain activity in peripuberty stressed rats are similar to neuroimaging observations in humans presenting the MAO_A allelic variant that is associated with an enhanced risk for impulsive–aggressive behaviour (54,172). Taken together, these data highlight the key role of neurobiological factors elicited by peripubertal adverse experiences for the emergence of violent behaviours.

Conclusions

Exposure of rats to fear-inducing, stressful experiences during the peripubertal period is a recently developed animal model for pathological aggression with face, construct and predictive validity (150,151). Face validity relates to the heightened attacks exhibited by peripuberty stressed male rats against nonthreatening conspecific individuals and, particularly, by their persistent attacks even when opponents display defensive behaviour because this pattern resembles key features in human impulsive aggression. Construct validity is supported by the reproduction of some of the key alterations in brain functioning observed in aggressive-impulsive human individuals, such as changes in the amygdala–medial orbitofrontal cortex circuitry (173,174), increases in the testosterone/corticosterone ratio (168) and alterations in the serotonergic system (175). Predictive validity is provided by the effectiveness of the treatment with a MAO_A inhibitor in reducing aggression, as also found in humans. Therefore, this animal model of peripubertal stress-induced adult aggression represents a valuable opportunity for the study of the neurobiological mechanisms sustaining violent behaviours, as well as for the development of novel therapeutic treatments.

Overall conclusions

The human findings and laboratory models reviewed here converge in the view that aggression-related problems result from developmental factors. There is, however, a fundamental difference

Table 2. A Summary of Adult Brain Alterations Following the Administration of Early Stressors.

Brain areas	RMS	PwSI	pPS	
PFC				
IL		Volume↓, activity ↑	↔	MAOA ↑
PrL		Volume↓, activity ↑	↔	
1Cg		↑	↔	
MO		↑	↓	
VO		↔	↔	
LO		↑	↔	
AI	OXT ↑			
Pir	AVP↑			
LS	AVP ↑ OXT ↓	↔	↔	
extAMY				
BNST	AVP ↓	↑	↔	
BLA		↑	↑	
MeA		↑	↑	
CeA		↔	↑	
HYP				
HAA	5-HT ↓ OXT ↓	↑		
LH	AVP↑	↔		
PAG			↔	

↑, increase; ↓, decrease; ↔, no change; empty cells: not investigated so far; when particularities are indicated, the change refers to that particular process or particularity. Otherwise, arrows indicate general changes in activity as measured by different means (mainly c-Fos immunocytochemistry). 5-HT, serotonergic neurotransmission, AI, agranular insular cortex, AVP, vasopressin neurotransmission, BLA, basolateral amygdala, BNST, bed nucleus stria terminalis, CeA, central amygdala, CG1, anterior cingular cortex, extAMY, extended amygdala; HAA, hypothalamic attack area (including the anterior and mediobasal HYP); HYP, hypothalamus; IL, infralimbic cortex, LH, lateral hypothalamus, LO, lateral orbitofrontal cortex; LS, lateral septum, MAO_A, monoamino oxidase A, MeA, medial amygdala, MO, medial orbitofrontal cortex, OXT, oxitocin neurotransmission, PFC, prefrontal cortex, Pir, piriform cortex, PAG, periaqueductal gray, pPS, peripubertal stress, PrL, pelimbic cortex, PwSI, post-weaning social isolation, RMS, repeated maternal separation; VO, ventral orbitofrontal cortex.

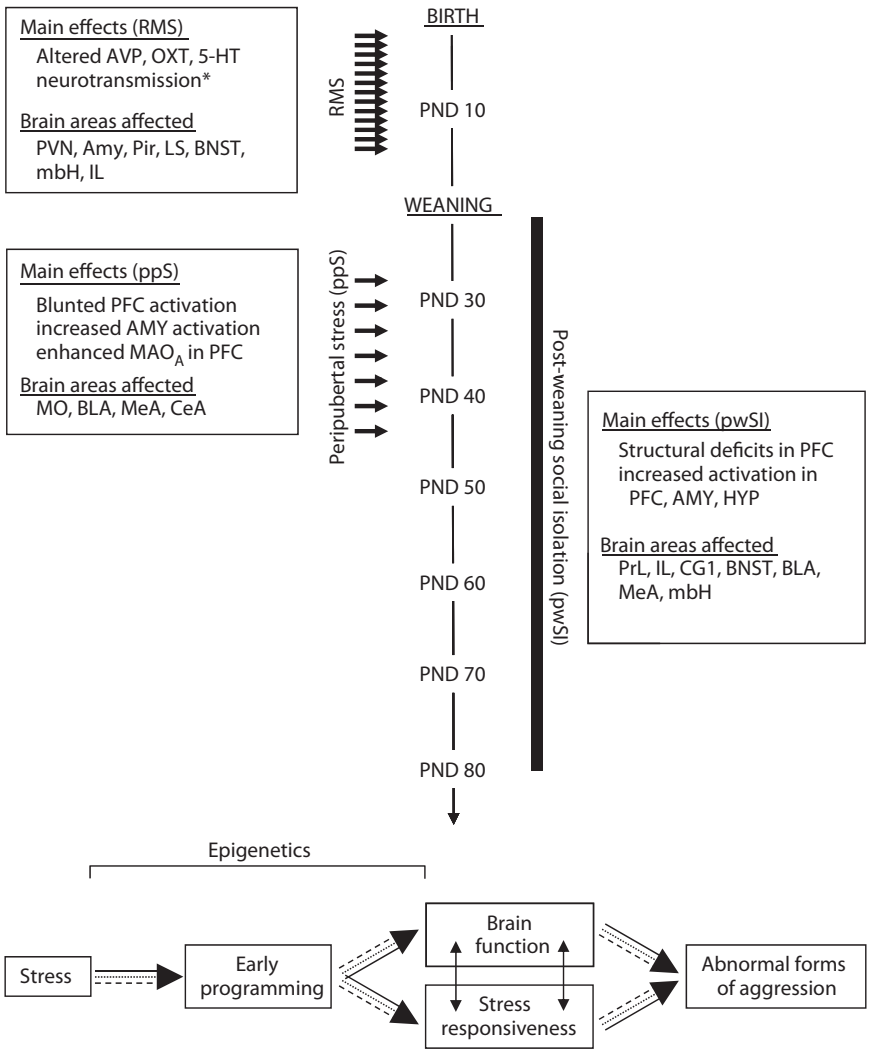

Fig. 1. Schematic illustration of the effects of early-life stress. Upper panel: stress protocols and the main alterations in brain function. Arrows and the vertical black bar indicate the periods when stressors were administered. For more details on brain function, see Table 2. Lower panel: suggested chain of events relating early-life stress and abnormal manifestations of aggression. The triple arrows illustrate the multiplicity of mechanisms that link early stressors and adult aggressiveness. 5-HT, serotonergic neurotransmission, AI, agranular insular cortex, AMY, amygdala, AVP, arginine vasopressin, BLA, basolateral amygdala, BNST, bed nucleus stria terminalis, CeA, central amygdala, CG1, anterior cingular cortex, HYP, hypothalamus, IL, infralimbic cortex, LH, lateral hypothalamus, LS, lateral septum, MAO_A, monoamino oxidase A, mbH, mediobasal hypothalamus (hypothalamic attack area), MeA, medial amygdala, MO, medial orbitofrontal cortex, OXT, oxytocin, PFC, prefrontal cortex, Pir, piriform cortex, PND, postnatal day, ppS, peripubertal stress, PrL, pelimbic cortex, pwSI, post-weaning social isolation, RMS, repeated maternal separation, * (RMS box), the direction of change is brain area-dependent.

between abnormal rodent aggression and escalated human aggression. Each animal model employs one single aetiological factor and studies its consequences for behaviour, emotionality and brain function. In other words, animal models dissect aetiological factors and study them separately. In addition, the relatively homogenous genetic background of subjects and their standardised maintenance considerably decreases individual variability, which allows focused studies on particular phenomena. This is impossible in humans, where various aetiological factors almost always occur in combinations (those who are neglected as children may also be exposed to stressors in puberty; moreover, they are at risk of using drugs at this age) and where genetic, educational and social influences are highly diverse.

One of the main conclusions of the present review is that each aetiological factor modelled (maternal neglect, early social neglect and peripubertal stressors) is sufficient by itself to induce the development of abnormal forms of aggression, to alter emotionality in general, as well as emotions associated with aggression, and to affect brain mechanisms associated with the display of aggressive behaviour (Tables 1 and 2). The second conclusion is that, although overlaps between models are evident, important differences were also observed. Repeated maternal separation appears to affect a wide range of emotional behaviours. Although its effects on aggression are relatively modest, it strongly increases anxiety-like and depression-like behaviours. These behavioural changes develop against the background of a complex array of changes in vasopressinergic,

oxytocinergic and serotonergic neurotransmission (a summary of the models and the main findings on brain mechanisms are provided in Fig. 1). Post-weaning social isolation leads to the development of a series of abnormal aggression features on the background of dramatically increased glucocorticoid and autonomic stress responses but without affecting anxiety-like and depression-like behaviours. At the neural level, these behavioural changes are accompanied by structural deficits in the medial prefrontal cortex but an aggression-induced increase in the activation of both the prefrontal cortex and amygdala. Peripubertal stressors also lead to abnormal aggression but without major changes in stress responses; moreover, a relative decrease in stress responsiveness was noted with this model. The decrease in stress responsiveness was more dramatic in the 'social variant' (early subjugation) and the 'corticosterone variant' (pubertal corticosterone administration) of the model (117,155). Behavioural and emotional alterations were accompanied by blunted orbitofrontal but increased amygdala activation during aggressive encounters. Although the models presented here (and abnormal aggression models in general) are in different stages of characterisation (a series of issues remained unstudied in each), the differences noted so far are sufficient *per se* to conclude that there are several emotional/neurobiological 'roads' to abnormal aggression in rodents, with these being aetiological factor-dependent.

The idea that different forms of abnormal aggression have differential neural underpinnings transpires from recent models of human aggression as well (56, 57, 59). Thus, the findings obtained in both animals and humans suggest that the idea of finding a single particular mechanism for abnormal aggression should be abandoned; dissecting the roles and effects of individual aetiological factors and integrating these findings into complex models remains an important task for the future. The analytical (aetiological factor-dissecting) nature of animal studies may become both exploratory and explanatory for particular aspects of human aggression. The integrating (multiple factor-encompassing) nature of human studies may be exploited to understand the complexity of phenomena underlying escalated aggression. Analytical and integrating approaches fortunately complement each other in general, and their combined application may elevate the understanding of abnormal aggression at new levels.

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References

1 Slutske WS. The genetics of antisocial behaviour. *Curr Psychiatry Rep* 2001; **3**: 158–162.
2 Moffitt TE. Genetic and environmental influences on antisocial behaviours: evidence from behavioural-genetic research. *Adv Genet* 2005; **55**: 41–104.
3 Craig IW. The importance of stress and genetic variation in human aggression. *BioEssays* 2007; **29**: 227–236.
4 Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science* 2002; **297**: 851–854.
5 McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342–348.
6 McCrory E, De Brito SA, Viding E. The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Front Psychiatry* 2011; **2**: 48.
7 Maccari S, Krugers HJ, Morley-Fletcher S, Szyf M, Brunton PJ. The consequences of early life adversity: neurobiological, behavioural and epigenetic adaptations. *J Neuroendocrinol.* 2014; **26**: 707–723.
8 Anderson NE, Kiehl KA. The psychopath magnetized: insights from brain imaging. *Trends Cogn Sci* 2012; **16**: 52–60.
9 Haller J, Kruk MR. Normal and abnormal aggression: human disorders and novel laboratory models. *Neurosci Biobehav Rev* 2006; **30**: 292–303.
10 Miczek KA, de Boer SF, Haller J. Excessive aggression as model of violence: a critical evaluation of current preclinical methods. *Psychopharmacology* 2013; **226**: 445–458.
11 Kazdin A. *Conduct disorders in childhood and adolescence*. 2nd edn. Thousand Oaks, CA: Sage, 1995.
12 Ford T. Practitioner review: how can epidemiology help us plan and deliver effective child and adolescent mental health services? *J Child Psychol Psychiatr* 2008; **49**: 900–914.
13 Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychol Bull* 2002; **128**: 746–773.
14 Patterson GR. *Coercive Family Process*. Eugene, OR: Castalia, 1982.
15 Stover CS, Connell C, Leve LD, Neiderhiser JM, Shaw DS, Scaramella L, Reiss D. Fathering and mothering in the family system: linking marital hostility and aggression in adopted toddlers. *J Child Psychol Psychiatry* 2012; **53**: 401–409.
16 Caspi A, Moffitt TE, Newman DL, Silva PA. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Arch Gen Psychiatry* 1996; **53**: 1033–1039.
17 Shaw DS, Lacourse E, Nagin DS. Developmental trajectories of conduct problems and hyperactivity from ages 2 to 10. *J Child Psychol Psychiatry* 2005; **46**: 931–942.
18 Shaw DS, Gilliom M, Ingoldsby EM, Nagin DS. Trajectories leading to school-age conduct problems. *Dev Psychol* 2003; **39**: 189–200.
19 Nigg JT. Temperament and developmental psychopathology. *J Child Psychol Psychiatry* 2006; **47**: 395–422.
20 Mesman J, Bongers IL, Koot HM. Preschool developmental pathways to preadolescent internalizing and externalizing problems. *J Child Psychol Psychiatry* 2001; **42**: 679–689.
21 Campbell SB, Shaw DS, Gilliom M. Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Dev Psychopathol* 2000; **12**: 467–488.
22 Van Goozen SHM, Fairchild G, Snoek H, Harold GT. The evidence for a neurobiological model of childhood antisocial behavior. *Psychol Bull* 2007; **133**: 149–182.
23 Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissing, suppressive, stimulatory, and preparative actions. *Endocr Rev* 2000; **21**: 55–89.
24 Del Giudice M, Ellis BJ, Shirtcliff EA. The adaptive calibration model of stress responsivity. *Neurosci Biobehav Rev* 2011; **35**: 1562–1592.
25 Laurent HK, Leve L, Neiderhiser J, Natsuaki M, Shaw D, Harold G, Reiss D. Effects of prenatal and postnatal parent depressive symptoms on adopted child HPA regulation: independent and moderated influences. *Dev Psychol* 2013; **49**: 876–886.
26 Bergman B, Brismar B. Hormone levels and personality traits in abusive and suicidal male alcoholics. *Alcohol Clin Exp Res* 1994; **18**: 311–316.

27 Van Goozen S, Fairchild G, Harold GT. The role of neurobiological deficits in childhood antisocial behavior. *Curr Dir Psychol Sci* 2008; **17**: 224–228.
28 Van Goozen SHM, Cohen-Kettenis PT, Snoek H, Matthys W, Swaab-Barneveld H, Van Engeland H. Executive functioning in children: a comparison of hospitalized ODD and ODD/ADHD children and normal controls. *J Child Psychol Psychiatry* 2004; **45**: 284–292.
29 Azar R, Zoccolillo M, Paquette D, Quiros E, Baltzer F, Tremblay RE. Cortisol levels and conduct disorder in adolescent mothers. *J Am Acad Child Adolesc Psychiatry* 2004; **43**: 461–468.
30 Van Bokhoven I, Matthys W, Van Goozen SHM, Van Engeland H. Prediction of adolescent outcome in children with disruptive behaviour disorders: a study of neurobiological, psychological and family factors. *Eur Child Adolesc Psychiatry* 2005; **14**: 153–163.
31 Shoal GD, Giancola PR, Kirillova GP. Salivary cortisol, personality, and aggressive behavior in adolescent boys: a 5-year longitudinal study. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 1101–1107.
32 McBurnett K, Lahey BB, Rathouz PJ, Loeber R. Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. *Arch Gen Psychiatry* 2000; **57**: 38–43.
33 Vanyukov MM, Moss HB, Plail JA, Blackson T, Mezzich AC, Tarter RE. Antisocial symptoms in preadolescent boys and in their parents: associations with cortisol. *Psychiatry Res* 1993; **46**: 9–17.
34 Haller J. The glucocorticoid/aggression relationship in animals and humans: An analysis sensitive to behavioral characteristics, glucocorticoid secretion patterns, and neural mechanisms. *Curr Top Behav Neurosci* 2014; . Feb 11. [Epub ahead of print] PMID: 24515548.
35 McElwain NL, Halberstadt AG, Volling BL. Mother- and father-reported reactions to children's negative emotions: relations to young children's emotional understanding and friendship quality. *Child Dev* 2007; **78**: 1407–1425.
36 Yap MBH, Allen NB, Ladouceur CD. Maternal socialization of positive affect: the impact of invalidation on adolescent emotion regulation and depressive symptomatology. *Child Dev* 2008; **79**: 1415–1431.
37 Little C, Carter AS. Negative emotional reactivity and regulation in 12-month-olds following emotional challenge: contributions of maternal-infant emotional availability in a low-income sample. *Infant Ment Health J* 2005; **26**: 354–368.
38 Degnan KA, Calkins SD, Keane SP, Hill-Soderlund AL. Profiles of disruptive behavior across early childhood: contributions of frustration reactivity, physiological regulation, and maternal behavior. *Child Dev* 2008; **79**: 1357–1376.
39 Ingoldsby EM, Shaw DS, Owens EB, Winslow EB. A longitudinal study of interparental conflict, emotional and behavioral reactivity, and preschoolers' adjustment problems among low-income families. *J Abnorm Child Psychol* 1999; **27**: 343–356.
40 Tarullo AR, Gunnar MR. Child maltreatment and the developing HPA axis. *Horm Behav* 2006; **50**: 632–639.
41 Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry* 2001; **49**: 1023–1039.
42 Harden KP, Turkheimer E, Emery RE, D'Onofrio BM, Slutske WS, Heath AS, Martin NG. Marital conflict and conduct problems in children of twins. *Child Dev* 2007; **78**: 1–18.
43 Shaw DS, Bell RQ. Developmental theories of parental contributors to antisocial behavior. *J Abnorm Child Psychol* 1993; **21**: 493–518.
44 Caspi A, Henry B, McGee RO, Moffitt TE, Silva PA. Temperamental origins of child and adolescent behavior problems: from age 3 to age 15. *Child Dev* 1995; **66**: 55–68.
45 Henggeler SW, Schoenwald SK. Evidence-based interventions for juvenile offenders and juvenile justice policies that support them. *Soc Res Child Develop* 2001; **25**: 1–20.
46 Watt MJ, Burke AR, Renner KJ, Forster GL. Adolescent male rats exposed to social defeat exhibit altered anxiety behavior and limbic monoamines as adults. *Behav Neurosci* 2009; **123**: 564–576.
47 Chapple CL, Tyler KA, Bersani BE. Child neglect and adolescent violence: examining the effects of self-control and peer rejection. *Violence Vict* 2005; **20**: 39–53.
48 Susman EJ. Psychobiology of persistent antisocial behavior: stress, early vulnerabilities and the attenuation hypothesis. *Neurosci Biobehav Rev* 2006; **30**: 376–389.
49 Kotch JB, Lewis T, Hussey JM, English D, Thompson R, Litrownik AJ, Runyan DK, Bangdiwala SI, Margolis B, Dubowitz H. Importance of early neglect for childhood aggression. *Pediatrics* 2008; **121**: 725–731.
50 Jonson-Reid M, Presnall N, Drake B, Fox L, Bierut L, Reich W, Kane P, Todd RD, Constantino JN. Effects of child maltreatment and inherited liability on antisocial development: an official records study. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 321–332.
51 Kim J, Cicchetti D. Longitudinal pathways linking child maltreatment, emotion regulation, peer relations, and psychopathology. *J Child Psychol Psychiatry* 2010; **51**: 706–716.
52 Nesdale D, Duffy A. Social identity, peer group rejection, and young children's reactive, displaced, and proactive aggression. *Br J Dev Psychol* 2011; **29**: 823–841.
53 Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neurosci* 1999; **2**: 1032–1037.
54 Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation—a possible prelude to violence. *Science* 2000; **289**: 591–594.
55 Herpertz SC, Sass H. Emotional deficiency and psychopathy. *Behav Sci Law* 2000; **18**: 567–580.
56 Berdahl CH. A neural network model of borderline personality disorder. *Neural Netw* 2010; **23**: 177–188.
57 Blair RJ. Psychopathy, frustration, and reactive aggression: the role of ventromedial prefrontal cortex. *Br J Psychol* 2010; **101**: 383–399.
58 Potegal M. Temporal and frontal lobe initiation and regulation of the top-down escalation of anger and aggression. *Behav Brain Res* 2012; **231**: 386–395.
59 Lopez NL, Vazquez DM, Olson SL. An integrative approach to the neurophysiological substrates of social withdrawal and aggression. *Dev Psychopathol* 2004; **16**: 69–93.
60 Harold GT, Rice FJ, Hay DF, Boivin J, van den Bree M, Thapar A. Familial transmission of depression and antisocial behaviour symptoms: disentangling the contribution of inherited and environmental factors and testing the mediating role of parenting. *Psychol Med* 2011; **22**: 1–11.
61 Harold GT, Leve LD, Barrett D, Elam K, Neiderhiser JM, Natsuaki MN, Shaw DS, Reiss D, Thapar A. Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture. *J Child Psychol Psychiatry* 2013; **54**: 1038–1046.
62 Braun K, Champagne FA. Paternal influences on offspring development: Behavioural and epigenetic pathways. *J Neuroendocrinol* 2014; **26**: 697–706.
63 Levine S. Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. *Eur J Pharmacol* 2000; **405**: 149–160.
64 Lehmann J, Russig H, Feldon J, Pryce CR. Effect of a single maternal separation at different pup ages on the corticosterone stress response in adult and aged rats. *Pharmacol Biochem Behav* 2002; **73**: 141–145.
65 Schmidt M, Enthoven L, van Woezik JH, Levine S, de Kloet ER, Oitzl MS. The dynamics of the hypothalamic–pituitary–adrenal axis during maternal deprivation. *J Neuroendocrinol* 2004; **16**: 52–57.

66 Pryce CR, Bettschen D, Nanz-Bahr NI, Feldon J. Comparison of the effects of early handling and early deprivation on conditioned stimulus, context, and spatial learning and memory in adult rats *Behav Neurosci* 2003; **117**: 883–893.
67 Ruedi-Bettschen D, Zhang W, Russig H, Ferger B, Weston A, Pedersen EM, Feldon J, Pryce CR. Early deprivation leads to altered behavioural, autonomic and endocrine responses to environmental challenge in adult Fischer rats. *Eur J Neurosci* 2006; **24**: 2879–2893.
68 Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats*Brain Res Mol* 1993; **18**: 195–200.
69 Wigger A, Neumann ID. Periodic maternal deprivation induces gender dependent alterations in behavioral and neuroendocrine responses to emotional stress in adult rats. *Physiol Behav* 1999; **66**: 293–302.
70 Liu D, Caldji C, Sharma S, Plotsky PM, Meaney MJ. Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinepherine release in the hypothalamic paraventricular nucleus. *J Neuroendocrinol* 2000; **12**: 5–12.
71 Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ. Early life programming and neurodevelopmental disorders. *Biol Psychiatry* 2010; **68**: 314–319.
72 Loi M, Koricka S, Lucassen PJ, Joëls M. Age- and sex-dependent effects of early life stress on hippocampal neurogenesis. *Front Endocrinol (Lausanne)* 2014; **5**: 13.
73 Neumann ID, Wigger A, Kromer S, Frank E, Landgraf R, Bosch OJ. Differential effects of periodic maternal separation on adult stress coping in a rat model of extremes in trait anxiety. *Neuroscience* 2005; **132**: 867–877.
74 Kember RL, Dempster EL, Lee TH, Schalkwyk LC, Mill J, Fernandes C. Maternal separation is associated with strain-specific responses to stress and epigenetic alterations to Nr3c1, Avp, and Nr4a1 in mouse. *Brain Behav* 2012; **2**: 455–467.
75 Kundakovic M, Lim S, Gudsnuk K, Champagne FA. Sex-specific and strain-dependent effects of early life adversity on behavioral and epigenetic outcomes. *Front Psychiatry* 2013; **4**: 78.
76 Lehmann J, Feldon J. Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing? *Rev Neurosci* 2000; **11**: 383–408.
77 Millstein RA, Holmes A. Effects of repeated maternal separation on anxiety- and depression-related phenotypes in different mouse strains. *Neurosci Biobehav Rev* 2007; **31**: 3–17.
78 Meaney MJ, Stewart J, Poulin P, McEwen BS. Sexual differentiation of social play in rat pups is mediated by the neonatal androgen-receptor system. *Neuroendocrinology* 1983; **37**: 85–90.
79 Panksepp J, Siviy S, Normansell L. The psychobiology of play: theoretical and methodological perspectives. *Neurosci Biobehav Rev* 1984; **8**: 465–492.
80 Vanderschuren LJ, Niesink RJ, Van Ree JM. The neurobiology of social play behavior in rats. *Neurosci Biobehav Rev* 1997; **21**: 309–326.
81 Pellis SM, Pellis VC. Play fighting of rats in comparative perspective: a schema for neurobehavioral analyses. *Neurosci Biobehav Rev* 1998; **23**: 87–101.
82 Veenema AH, Neumann ID. Maternal separation enhances offensive play-fighting, basal corticosterone and hypothalamic vasopressin mRNA expression in juvenile male rats. *Psychoneuroendocrinology* 2009; **34**: 463–467.
83 Veenema AH, Blume A, Niederle D, Buwalda B, Neumann ID. Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. *Eur J Neurosci* 2006; **24**: 1711–1720.
84 Veenema AH, Bredewold R, Neumann ID. Opposite effects of maternal separation on intermale and maternal aggression in C57BL/6 mice: link to hypothalamic vasopressin and oxytocin immunoreactivity. *Psychoneuroendocrinology* 2007; **32**: 437–450.
85 Tsuda MC, Yamaguchi N, Ogawa S. Early life stress disrupts peripubertal development of aggression in male mice. *NeuroReport* 2011; **22**: 259–263.
86 Caldji C, Francis D, Sharma S, Plotsky PM, Meaney MJ. The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology* 2000; **22**: 219–229.
87 Huot RL, Thrivikrama KV, Meaney MJ, Plotsky PM. Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. *Psychopharmacology* 2001; **158**: 366–373.
88 Kalinichev M, Easterling KW, Plotsky PM, Holtzman SG. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long-Evans rats. *Pharmacol Biochem Behav* 2002; **73**: 131–140.
89 Romeo RD, Mueller A, Sisti HM, Ogawa S, McEwen BS, Brake WG. Anxiety and fear behaviors in adult male and female C57BL/6 mice are modulated by maternal separation. *Horm Behav* 2003; **43**: 561–567.
90 Aisa B, Tordera R, Lasheras B, Del Rio J, Ramirez MJ. Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology* 2007; **32**: 256–266.
91 MacQueen GM, Ramakrishnan K, Ratnasingan R, Chen B, Young LT. Desipramine treatment reduces the long-term behavioural and neurochemical sequelae of early-life maternal separation. *Int J Neuropsychopharmacol* 2003; **6**: 391–396.
92 Veenema AH, Reber SO, Selch S, Obermeier F, Neumann ID. Early life stress enhances the vulnerability to chronic psychosocial stress and experimental colitis in adult mice. *Endocrinology* 2008; **149**: 2727–2736.
93 Murgatroyd C, Wigger A, Frank E, Singewald N, Bunck M, Holsboer F, Landgraf R, Spengler D. Impaired repression at a vasopressin promoter polymorphism underlies overexpression of vasopressin in a rat model of trait anxiety. *J Neurosci* 2004; **24**: 7762–7770.
94 Franklin TB1, Linder N, Russig H, Thöny B, Mansuy IM. Influence of early stress on social abilities and serotonergic functions across generations in mice. *PLoS ONE* 2011; **6**: e21842.
95 Suri D, Veenit V, Sarkar A, Thiagarajan D, Kumar A, Nestler EJ, Galande S, Vaidya VA. Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. *Biol Psychiatry* 2013; **73**: 658–666.
96 Gardner KL, Thrivikraman KV, Lightman SL, Plotsky PM, Lowry CA. Early life experience alters behavior during social defeat: focus on serotonergic systems. *Neuroscience* 2005; **136**: 181–191.
97 De Kloet ER, Rots NY, Cools AR. Brain-corticosteroid hormone dialogue: slow and persistent. *Cell Mol Neurobiol* 1996; **16**: 345–356.
98 Haller J, Millar S, van de Schraaf J, de Kloet RE, Kruk MR. The active phase-related increase in corticosterone and aggression are linked. *J Neuroendocrinol* 2000; **12**: 431–436.
99 Haller J, Halasz J, Mikics E, Kruk MR, Makara GB. Ultradian corticosterone rhythm and the propensity to behave aggressively in male rats. *J Neuroendocrinol* 2000; **12**: 937–940.
100 Haller J, Halász J, Mikics E, Kruk MR. Chronic glucocorticoid deficiency-induced abnormal aggression, autonomic hypoarousal, and social deficit in rats. *J Neuroendocrinol* 2004; **16**: 550–557.
101 Kruk MR, Halasz J, Meelis W, Haller J. Fast positive feedback between the adrenocortical stress response and a brain mechanism involved in aggressive behavior. *Behav Neurosci* 2004; **118**: 1062–1070.

102 Mikics E, Kruk MR, Haller J. Genomic and non-genomic effects of glucocorticoids on aggressive behavior in male rats. *Psychoneuroendocrinology* 2004; **29**: 618–635.

103 Donaldson ZR, Young LJ. Oxytocin, vasopressin, and the neurogenetics of sociality. *Science* 2008; **322**: 900–904.

104 Goodson JL. Nonapeptides and the evolutionary patterning of sociality. *Prog Brain Res* 2008; **170**: 3–15.

105 Neumann ID. The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood. *Front Neuroendocrinol* 2009; **30**: 483–496.

106 Lukas M, Neumann ID. Oxytocin and vasopressin in rodent behaviors related to social dysfunctions in autism spectrum disorders. *Behav Brain Res* 2013; **251**: 85–94.

107 Calcagnoli F, de Boer SF, Althaus M, den Boer JA, Koolhaas JM. Antiaggressive activity of central oxytocin in male rats. *Psychopharmacology* 2013; **229**: 639–651.

108 Lukas M, Bredewold R, Neumann ID, Veenema AH. Maternal separation interferes with developmental changes in brain vasopressin and oxytocin receptor binding in male rats. *Neuropharmacology* 2010; **58**: 78–87.

109 Tribollet E, Goumaz M, Raggenbass M, Dubois-Dauphin M, Dreifuss JJ. Early appearance and transient expression of vasopressin receptors in the brain of rat fetus and infant. An autoradiographical and electrophysiological study. *Brain Res Dev Brain Res* 1991; **58**: 13–24.

110 Compaan JC, Buijs RM, Pool CW, De Ruiter AJ, Koolhaas JM. Differential lateral septal vasopressin innervation in aggressive and nonaggressive male mice. *Brain Res Bull* 1993; **30**: 1–6.

111 Everts HG, De Ruiter AJ, Koolhaas JM. Differential lateral septal vasopressin in wild-type rats: correlation with aggression. *Horm Behav* 1997; **31**: 136–144.

112 Beiderbeck DI, Neumann ID, Veenema AH. Differences in intermale aggression are accompanied by opposite vasopressin release patterns within the septum in rats bred for low and high anxiety. *Eur J Neurosci* 2007; **26**: 3597–3605.

113 Neumann ID, Veenema AH, Beiderbeck DI. Aggression and anxiety: social context and neurobiological links. *Front Behav Neurosci* 2010; **4**: 12.

114 Veenema AH, Torner L, Blume A, Beiderbeck DI, Neumann ID. Low inborn anxiety correlates with high intermale aggression: link to ACTH response and neuronal activation of the hypothalamic paraventricular nucleus. *Horm Behav* 2007; **51**: 11–19.

115 Beiderbeck DI, Reber SO, Havasi A, Bredewold R, Veenema AH, Neumann ID. High and abnormal forms of aggression in rats with extremes in trait anxiety - Involvement of the dopamine system in the nucleus accumbens. *Psychoneuroendocrinology* 2012; **37**: 1969–1980.

116 De Jong TR, Beiderbeck DI, Neumann ID. Brain oxytocin inhibits female aggressive behavior in a novel female intruder test. PLoS One. 2014 Mar 10;9(3):e91701. doi: 10.1371/journal.pone.0091701

116a Harlow HF, Dodsworth RO, Harlow MK. Total social isolation in monkeys. *Proc Nat Acad Sci USA* 1965; **54**: 90–97.

117 Delville Y, Melloni RH Jr, Ferris CF. Behavioral and neurobiological consequences of social subjugation during puberty in golden hamsters. *J Neurosci* 1998; **18**: 2667–2672.

118 Lesch KP. When the serotonin transporter gene meets adversity: the contribution of animal models to understanding epigenetic mechanisms in affective disorders and resilience. *Curr Top Behav Neurosci* 2011; **7**: 251–280.

119 Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD. Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry* 2002; **7**: 118–122.

120 Reif A, Rosler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, Lesch KP, Retz W. Nature and nurture predispose to violent behavior: serotonergic genes and adverse childhood environment. *Neuropsychopharmacology* 2007; **32**: 2375–2383.

121 Olivier B, Mos J. Serenics, serotonin and aggression. *Prog Clin Biol Res* 1990; **361**: 203–230.

122 Ferris CF, Delville Y. Vasopressin and serotonin interactions in the control of agonistic behavior. *Psychoneuroendocrinology* 1994; **19**: 593–601.

123 Ferris CF. Serotonin diminishes aggression by suppressing the activity of the vasopressin system. *Ann NY Acad Sci* 1996; **794**: 98–103.

124 Ferris CF, Stolberg T, Delville Y. Serotonin regulation of aggressive behavior in male golden hamsters (*Mesocricetus auratus*). *Behav Neurosci* 1999; **113**: 804–815.

125 Tulogdi A, Toth M, Barsvari B, Biro L, Mikics E, Haller J. Effects of resocialization on post-weaning social isolation-induced abnormal aggression and social deficits in rats. *Dev Psychobiol* 2014; **56**: 49–57.

126 Day HD, Seay BM, Hale P, Hendricks D. Early social deprivation and the ontogeny of unrestricted social behavior in the laboratory rat. *Dev Psychobiol* 1982; **15**: 47–59.

127 Toth M, Halász J, Mikics E, Barsy B, Haller J. Early social deprivation induces disturbed social communication and violent aggression in adulthood. *Behav Neurosci* 2008; **122**: 849–854.

128 Haller J. The neurobiology of abnormal manifestations of aggression – a review of hypothalamic mechanisms in cats, rodents, and humans. *Brain Res Bull* 2013; **93**: 97–109.

129 Wall VL, Fischer EK, Bland ST. Isolation rearing attenuates social interaction-induced expression of immediate early gene protein products in the medial prefrontal cortex of male and female rats. *Physiol Behav* 2012; **107**: 440–450.

130 Workman JL, Fonken LK, Gusfa J, Kassouf KM, Nelson RJ. Post-weaning environmental enrichment alters affective responses and interacts with behavioral testing to alter nNOS immunoreactivity. *Pharmacol Biochem Behav* 2011; **100**: 25–32.

131 Bibancos T, Jardim DL, Aneas I, Chiavegatto S. Social isolation and expression of serotonergic neurotransmission-related genes in several brain areas of male mice. *Genes Brain Behav* 2007; **6**: 529–539.

132 Shimozuru M, Kikusui T, Takeuchi Y, Mori Y. Effects of isolation-rearing on the development of social behaviors in male Mongolian gerbils (*Meriones unguiculatus*). *Physiol Behav* 2008; **94**: 491–500.

133 Toth M, Mikics E, Tulogdi A, Aliczki M, Haller J. Post-weaning social isolation induces abnormal forms of aggression in conjunction with increased glucocorticoid and autonomic stress responses. *Horm Behav* 2011; **60**: 28–36.

134 Weiss IC, Pryce CR, Jongen-Rêlo AL, Nanz-Bahr NI, Feldon J. Effect of social isolation on stress-related behavioural and neuroendocrine state in the rat. *Behav Brain Res* 2004; **152**: 279–295.

135 Mikics E, Alicki M, Haller J. The effects of post-weaning social isolation on challenge responding in social and non-social behavioral tests. *Horm Behav* 2014; accepted for publication.

136 Fries AB, Shirtcliff EA, Pollak SD. Neuroendocrine dysregulation following early social deprivation in children. *Dev Psychobiol* 2008; **50**: 588–599.

137 Pesonen AK, Raikkonen K, Feldt K, Heinonen K, Osmond C, Phillips DI, Barker DJ, Eriksson JG, Kajantie E. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. *Psychoneuroendocrinology* 2010; **35**: 758–767.

138 Toth M, Tulogdi A, Biro L, Soros P, Mikics E, Haller J. The neural background of hyper-emotional aggression induced by post-weaning social isolation. *Behav Brain Res* 2012; **233**: 120–129.

139 Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Res* 2009; **174**: 81–88.

140 Lotze M, Veit R, Anders S, Birbaumer N. Evidence for a different role of the ventral and dorsal medial prefrontal cortex for social reactive aggression: an interactive fMRI study. *Neuroimage* 2007; **34**: 470–478.

141 New AS, Hazlett EA, Newmark RE, Zhang J, Triebwasser J, Meyerson D, Lazarus S, Trisdorfer R, Goldstein KE, Goodman M, Koenigsberg HW, Flory JD, Siever LJ, Buchsbaum MS. Laboratory induced aggression: a positron emission tomography study of aggressive individuals with borderline personality disorder. *Biol Psychiatry* 2009; **66**: 1107–1114.

142 Veit R, Lotze M, Sewing S, Missenhardt H, Gaber T, Birbaumer N. Aberrant social and cerebral responding in a competitive reaction time paradigm in criminal psychopaths. *Neuroimage* 2010; **49**: 3365–3372.

143 Strenziok M, Krueger F, Heinecke A, Lenroot RK, Knutson KM, van der Meer E, Grafman J. Developmental effects of aggressive behavior in male adolescents assessed with structural and functional brain imaging. *Soc Cogn Affect Neurosci* 2011; **6**: 2–11.

144 Montag C, Weber B, Trautner P, Newport B, Markett S, Walter NT, Felten A, Reuter M. Does excessive play of violent first-person-shooter-video-games dampen brain activity in response to emotional stimuli? *Biol Psychol* 2012; **89**: 107–111.

145 Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 2008; **9**: 947–957.

146 Blakemore SJ. Development of the social brain in adolescence. *J R Soc Med* 2012; **105**: 111–116.

147 Sachser N. The ability to arrange with conspecifics depends on social experiences around puberty. *Physiol Behav* 1993; **53**: 539–544.

148 Delville Y, David JT, Taravosh-Lahn K, Wommack JC. Stress and the development of agonistic behavior in golden hamsters. *Horm Behav* 2003; **44**: 263–270.

149 Wommack JC, Delville Y. Stress, aggression, and puberty: neuroendocrine correlates of the development of agonistic behavior in golden hamsters. *Brain Behav Evol* 2007; **70**: 267–273.

150 Cordero MI, Poirier GL, Marquez C, Veenit V, Fontana X, Salehi B, Ansermet F, Sandi C. Evidence for biological roots in the transgenerational transmission of intimate partner violence. *Transl Psychiatry* 2012; **2**: e106.

151 Marquez C, Poirier GL, Cordero MI, Larsen MH, Groner A, Marquis J, Magistretti PJ, Trono D, Sandi C. Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. *Transl Psychiatry* 2013; **3**: e216.

152 Cordero MI, Ansermet F, Sandi C. Long-term programming of enhanced aggression by peripuberty stress in female rats. *Psychoneuroendocrinology* 2013; **38**: 2758–2769.

153 Poirier GL, Cordero MI, Sandi C. Female vulnerability to the development of depression-like behavior in a rat model of intimate partner violence is related to anxious temperament, coping responses, and amygdala vasopressin receptor 1a expression. *Front Behav Neurosci* 2013; **7**: 35.

154 Weder N, Yang BZ, Douglas-Palumberi H, Massey J, Krystal JH, Gelernter J, Kaufman J. MAOA genotype, maltreatment, and aggressive behavior: the changing impact of genotype at varying levels of trauma. *Biol Psychiatry* 2009; **65**: 417–424.

155 Veenit V, Cordero MI, Tzanoulinou S, Sandi C. Increased corticosterone in peripubertal rats leads to long-lasting alterations in social exploration and aggression. *Front Behav Neurosci* 2013; **7**: 26.

156 Wommack JC, Salinas A, Melloni RH Jr, Delville Y. Behavioural and neuroendocrine adaptations to repeated stress during puberty in male golden hamsters. *J Neuroendocrinol* 2004; **16**: 767–775.

157 Wommack JC, Salinas A, Delville Y. Glucocorticoids and the development of agonistic behaviour during puberty in male golden hamsters. *J Neuroendocrinol* 2005; **17**: 781–787.

158 Johnson JG, Cohen P, Brown J, Smailes EM, Bernstein DP. Childhood maltreatment increases risk for personality disorders during early adulthood. *Arch Gen Psychiatr* 1999; **56**: 600–606.

159 Foy DW, Ritchie IK, Conway AH. Trauma exposure, posttraumatic stress, and comorbidities in female adolescent offenders: findings and implications from recent studies. *Eur J Psychotraumatol* 2012; **3**: doi:10.3402.

160 Toledo-Rodriguez M, Sandi C. Stress during adolescence increases novelty seeking and risk taking behavior in male and female rats. *Front Behav Neurosci* 2011; **7**: 5–17.

161 Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. *Dev Psychobiol* 2010; **52**: 671–690.

162 Patterson GR, Stoolmiller M. Replications of a dual failure model for boys' depressed mood. *J Consult Clin Psychol* 1991; **59**: 491–498.

163 Beach SR, Brody GH, Gunter TD, Packer H, Wernett P, Philibert RA. Child maltreatment moderates the association of MAOA with symptoms of depression and antisocial personality disorder. *J Fam Psychol* 2010; **24**: 12–20.

164 Hamilton LD, Newman ML, Delville CL, Delville Y. Physiological stress response of young adults exposed to bullying during adolescence. *Physiol Behav* 2008; **95**: 617–624.

165 Resnick HS, Yehuda R, Pitman RK, Foy DW. Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry* 1995; **152**: 1675–1677.

166 Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry* 1996; **40**: 79–88.

167 Trickett PK, Noll JG, Susman EJ, Shenk CE, Putnam FW. Attenuation of cortisol across development for victims of sexual abuse. *Dev Psychopathol* 2010; **22**: 165–175.

168 Terburg D, Morgan B, van Honk J. The testosterone–cortisol ratio: a hormonal marker for proneness to social aggression. *Int J Law Psychiatry* 2009; **32**: 216–223.

169 Toledo-Rodriguez M, Pitiot A, Paus T, Sandi C. Stress during puberty boosts metabolic activation associated with fear-extinction learning in hippocampus, basal amygdala and cingulate cortex. *Neurobiol Learn Mem* 2012; **98**: 93–101.

170 Raine A, Buchsbaum M, LaCasse L. Brain abnormalities in murderers indicated by positron emission tomography. *Biol Psychiatry* 1997; **42**: 495–508.

171 Raine A, Meloy JR, Bihrle S, Stoddard J, LaCasse L, Buchsbaum MS. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. *Behav Sci Law* 1998; **16**: 319–332.

172 Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri A, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci USA* 2006; **103**: 6269–6274.

173 Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biol Psychiatry* 2007; **62**: 168–178.

174 Coccaro EF, Sripada CS, Yanowitch RN, Phan KL. Corticolimbic function in impulsive aggressive behavior. *Biol Psychiatry* 2011; **69**: 1153–1159.

175 Buckholtz JW, Meyer-Lindenberg A. MAOA and the neurogenetic architecture of human aggression. *Trends Neurosci* 2008; **31**: 120–129.